

74. The method of claim 38, further comprising normalizing said electrochemiluminescence signal using a blank reactant mixture containing said reactant and said luminophore and not said reaction partner and exposing said blank reactant mixture to electrical energy and measuring emitted electrochemiluminescence signal thereby determining said time course of reaction.

75. The method of claim 74, further comprising normalizing said electrochemiluminescence signal using a second reaction mixture containing said reactant and said luminophore and wherein said second reaction mixture is allowed to react to completion prior to exposing said second reaction mixture to electrical energy and measuring said emitted electrochemiluminescence signal thereby determining said time course of reaction.--

REMARKS

Reconsideration and withdrawal of the rejections of the above-identified application are respectfully requested in view of the amendments and remarks herein. All of the issues objected to by the Examiner have been remedied.

Claims 1-70 are pending in this application. Claims 1-36 have been allowed by the Examiner. Claims 37, 38, 41, 42, 57, 62, 63, 65, 68, 69 and 70 have been amended to further the prosecution of the application. New claims 71-75 have been added to more particularly point out and distinctly define the invention. Support for the new claims is found throughout the disclosure of U.S. 5,527,710 particularly, column 2, lines 22-34; column 2, line 57 through column 3, line 3; and column 3 lines 26-33. No new matter has been added.

Commissioner is hereby authorized to charge \$45.00, the fee for a small entity, to **Deposit Account No. 50-0540** for the five (5) additional claims. No additional fee is believed necessary for entry and consideration of this amendment. However, the Commissioner is hereby authorized to charge any additional fee or credit any overpayment to the same account.

The following addresses each of the Examiner's objections or comments (shown in italics):

1. *The original patent, or affidavit or declaration as to loss or inaccessibility of the original patent, must be received before this reissue application can be allowed. See 37 CFR 1.178.*

We are presently searching for the original patent and will offer it for surrender before allowance.

2. *The September 28, 1999 response to the November 02, 1998 "Petition to Suspend the Rules Under 37 CFR 1.183" accorded Rule 1.47(a) status to this application.*

A copy of the response to the November 02, 1998 petition is enclosed indicating the petition was granted on September 28, 1999.

3. *Quotation of 35 U.S.C. 112.*

4. *Quotation of 37 CFR 1.71(a)-(c).*

5. *The specification is objected to under 37 CFR 1.71 because the specification, as originally filed, does not provide an enabling written description of nor support for the invention as it is now claimed. The invention as it is described in the specification is limited to a determination of the time course of a biomolecular reaction as set forth in the sequence of reaction steps recited in claims 1-36 of U.S. 5,527,710.*

This objection is addressed by Applicants' comments submitted in response to Paragraph No. 6 below.

6. *Claims 37-70 are rejected under U.S.C. 112, first paragraph, as not corresponding with the enabling written description of the invention as it is set forth in the specification (see paragraph 5. above). The specification, while being enabling for determining the time course of a biomolecular reaction as set forth in the sequence of reaction steps recited in claims 1-36 of U.S. 5,527,710, does not reasonably provide for nor a description of a process comprising simply reacting two members of a specific binding pair in the presence of a luminophore, inducing the luminophore to electrochemiluminescence and measuring the time course of the electrochemiluminescent reaction. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims. The invention, as it is described in the specification, requires that three separate reactions be carried out (pages 6-8 of the specification; claim 1: first reaction: steps (a) and (b); second reaction: steps (c) and (d); third reaction: steps (e) and (f) and that an algorithm be applied to compare the resulting electrochemiluminescent "values" for each of the three separate reactions to measure the time course of the biomolecular reaction (claim 1: steps (g) through (k).*

With respect to the aspect of the rejection relating to the claims which do not recite the presence of a luminophore, the claims have been amended to require the presence of a luminophore to further the prosecution of the application. Accordingly, applicants respectfully request that this aspect of the rejection be withdrawn.

In the Office Action, the Examiner asserts that "There is no indication in the specification that the broader concept as is now claimed was contemplated by the inventors". Contrary to the

Examiner's assertion, the specification discloses the subject matter set forth in the present claims. More specifically, the Examiner is directed to the Summary of the Invention in the specification of U.S. 5,527,710, first paragraph, where the broader generic concept is clearly contemplated and described by the inventors. The inventors disclose:

A biomolecular reaction which is to be monitored according to the present invention must be carried out using a luminophore under reaction conditions which will relate the concentration of a reactant or a product of the reaction to the ECL intensity. The reagents employed in the reaction, therefore, will include a reaction partner which reacts with the reactant and participates with the luminophore to cause the emission of ECL. Column 2, lines 22-29.

Clearly, this broad recitation discloses an embodiment of the invention which does not include a requirement for normalization or calibration. The language does not exclude the comparison of relative rates measured in unnormalized or uncalibrated systems. It also does not exclude the use of appropriate normalization or calibration procedures so as to define the exact relationship between ECL signal and the extent of a reaction, or to compensate for instrumental factors such as drift or background. The first paragraph of 35 U.S.C. §112 requires nothing more than objective enablement. Whether this is achieved by illustrative examples or by broad terminology is of no importance. *In re Marzocchi*, 169 U.S.P.Q. 367 (CCPA 1971).

Moreover, as the skill in the art is high with regards to normalization or calibration of assays, one of ordinary skill in the art would not require explicit disclosure of every suitable normalization or calibration procedure and/or step in order to practice the present invention. Such details are unnecessary as they are known in the art. The preferred embodiments described in U.S. 5,527,710 are particularly advantageous (but not required) approaches or methods of using controls to more accurately arrive at the correct ECL measurement of the absolute reaction. Applicants respectfully submit that one of ordinary skill in the art would clearly recognize the

presently claimed concept (e.g., determining the time course of reaction by measuring electrochemiluminescence) in view of the original disclosure.

Furthermore, Applicants urge that detailed procedures for making and using an invention may not be necessary if the description of the invention itself is sufficient to permit those skilled in the art to make and use the invention [MPEP §2164]. A patent does not teach, **and preferably omits**, what is well known in the art. *In re Buchner*, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 221 U.S.P.Q. 481, 489 (Fed. Cir. 1984). [See also, MPEP § 2164.01]. As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. § 112 is satisfied. *In re Fisher*, 166 U.S.P.Q. 18, 24 (CCPA 1970). See also, MPEP § 2164.01(b).

7. *Quotation of the second paragraph of 35 U.S.C. 112*

8. *Claims 37-70 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP sec 2172.01. The omitted steps are: the sequence of steps set forth in claim 1 of U.S. 5,527,710.*

With respect to the Examiner's allegation that the omission of steps results in indefinite claims, the present claims are clear and definite to one of ordinary skill in the art when properly construed in view of specification. Applicants submit that the breadth of a claim is not to be equated with indefiniteness. *In re Miller*, 169 U.S.P.Q. 597 (CCPA 1971) [See also, MPEP 2173.04]. A claim is indefinite only if it embraces what an applicant did not intend to claim or if

its scope takes on an unreasonable degree of uncertainty when construed in light of the prior art or the disclosure. *In re Cormany*, 177 U.S.P.Q. 450 (CCPA 1973).

Furthermore, Applicants refer to the comments set forth in number 6 above which also address this rejection under second paragraph of 35 U.S.C. 112.

Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. 112, second paragraph, be withdrawn.

9. *Claims 37-70 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for the following reasons.*

a. *Claims 37, 57 and 68 fail to define what the "reactant" is i.e. what it reacts with.*

Applicants submit that claims 37, 57 and 68 are clear and definite to one of ordinary skill in the art when properly construed in view of the specification. One of ordinary skill in the art would readily understand the meaning of these claims when properly construed in view of the specification and the prior art. The definiteness of claim language must be analyzed, not in a vacuum, but in light of (1) the content of the particular application disclosure, (2) the teachings of the prior art, and (3) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made (MPEP, Section 2173.02).

Applicants urge that if the scope of subject matter embraced by a claim is clear, and if the applicant has not otherwise indicated that he intends the claim to be of a different scope, then the claim particularly points out and distinctly claims the subject matter which the applicant regards as his invention. *In re Borkowski*, 164 U.S.P.Q. 642 (CCPA 1970); *In re Robins*, 166 U.S.P.Q. 552 (CCPA 1970).

With respect to claim 37, the claim does not require that the reactant react with anything. The reactant may, for example, decompose into a reaction product which increases or decreases the ECL signal. Therefore, the claim is clear and definite.

Claim 57 recites "the reactant and said reaction partner bind to form a complex" and claim 68 recites "the reactant reacts with the reaction partner to form a reaction product". Accordingly, one of ordinary skill in the art would readily understand the meaning of the term "reactants" when properly construed in view of the specification.

To further the prosecution of the application, claims 37, 57 and 68 have been amended to further define the invention. Applicants also refer the Examiner to the discussion set forth below in Section 9b.

b. In claim 37, it is unclear how the "reactant" and "luminophore" interact. Presumably the change in electrochemiluminescence of the "luminophore" is correlated with the formation of the "reaction product" but how this occurs is unclear. To what specific binding moiety is the "luminophore" attached? The same problem exists for claim 62 since it is unclear how the "luminophore" interacts with the enzyme and/or enzyme substrate.

Claim 37 is clear and definite to one of ordinary skill in the art when properly construed in view of the specification for the reasons set forth above in Section 9a. Applicants submit that one of ordinary skill in the art would understand how the reactant and luminophore interact and how the change in ECL is correlated with the formation of the reaction product (See, for example, Examples 1-5). Furthermore, Applicants respectfully submit that the luminophore may or may not be attached to the reactant or some other reaction component. The specification describes a variety of different formats for practicing the invention where the luminophore reacts with the reactant or the reaction product. As set forth in the present application, depending on

the type of embodiment that is used, the luminophore may be attached to or reacted with the reactant, reaction partner, or the reaction product to emit ECL. See column 2 lines 25-32, column 4, lines 20-25, 40-46, column 8, lines 38-41, among other areas of the specification.

Moreover, the specification includes several examples directed to different embodiments for practicing the invention.

Example 1 describes an enzymatic reaction where NADH (an ECL coreactant) is generated. The kinetics of the reaction were followed by monitoring the ECL output with time as NADH was generated and reacted with $\text{Ru}(\text{bpy})_3^{2+}$. Thus, Example 1 relates to a method where the luminophore is not attached to either reactant (e.g., the enzyme or the enzyme substrate). See also, Examples 2 and 3.

Example 4 relates to a method where the reaction of a reactant with a binding partner brings the luminophore into proximity to a magnetic particle held against an electrode which provides increased ECL efficiency (which increases the signal emitted). In this example, streptavidin coated beads combine with biotinylated DNA label during the reaction.

Example 5 describes an CEA antibody-antigen system where streptavidin-coated beads bound to a biotinylated CEA antigen subsequently binds to a labeled CEA specific antibody. In this example, the reaction rate measured is not the streptavidin-biotin reaction but the CEA antibody-antigen reaction.

Thus, Applicants respectfully submit that claim 37 is clear and definite when properly construed in view of the specification.

c. *In claims 41 and 42 it is unclear how the "reactant" or "reaction product" "participates with the luminophore in the electrochemiluminescent process."*

Claims 41 and 42 have been amended by replacing the term “participates” with “reacts” to further define the invention. The way luminophore reacts has been addressed in Sections 9a and 9b above.

d. Claim 68 inconsistently requires “measuring the electrochemiluminescence” when no electrochemiluminescent moiety is required to be present in the reaction “composition.”

Claim 68 has been amended to more clearly define the invention to further the prosecution of the application.

e. The claims fail to define the relationship between the times at which the composition is exposed to electrical energy and the times at which the electrochemiluminescence is measured (“different” times).

Applicants submit the claims are clear and definite to one of ordinary skill in the art when properly construed in view of the specification. One of ordinary skill in the art would readily understand in view of the teachings set forth in the specification and the prior art, that the measurement of electrochemiluminescence is taken simultaneously with the application of electrical energy. However, to further the prosecution of the application, the claims have been amended to more clearly define the invention.

f. In claim 38, “bimolecular” should be --biomolecular--.

Claim 38 has been amended to correct the typographical error as suggested by the Examiner.

10. Claims 37-39, 40-42, 47, 48, 51-58, 60, 61, and 68 are rejected under 35 U.S.C. §112, first paragraph, as being based on a non-enabling written description for the following reasons. For these claims, there is an inadequate enabling description in the specification to support the

scope of the term "reactant" which would include all types of reactions of organic and/or inorganic chemicals and not just reactions between specific binding pair members for which there is enablement in the specification.

The claims are fully enabled for the reasons set forth above in Sections 6, 9a and 9b. Clearly, the disclosure is not limited to "reactions between specific binding pair members" as suggested by the Examiner (See Examples 1-3). Moreover, the claims are limited to reactants which form reaction products where the reaction progress may be measured using electrochemiluminescence. Thus, the claims exclude reactants which are not enabled (e.g., reactants which do not form reaction products according to a reaction which can be measured by ECL).

To further the prosecution of the application, the claims have been amended to further define the invention.

11. *Quotation of 35 U.S.C. 102*

12. *Quotation of 35 U.S.C. 103(a)*

13. *Claims 37-39, 41, 42, 49, 51-54, 57, 59, 60, and 68-70 are rejected under 35 U.S.C. 102(b) as anticipated by Shibue et al. (West abstract of EP500,305A2). Shibue et al describe a method of measuring an immunoreactant comprising reacting a member of a specific binding pair with its specific binding partner which has been immobilized on insoluble carrier particles and labeled with an electrochemiluminescent label, inducing the label to chemiluminescence by activation with electric voltage and measuring the time course of the reaction (i.e. the change in concentration of the immunoreactant). This method anticipates the method of instant claim 37 which involves the same steps as the Shibue et al process.*

The Shibue et al. reference does not anticipate the above claims. In order to anticipate a claim, the cited reference must disclose each and every limitation in the claim (MPEP 2131). Shibue et al. fails to disclose the presently claimed methods of determining the time course of reaction.

Applicants respectfully submit that the Examiner has misinterpreted the reference. Shibue et al. describes an ECL assay characterized by a high rate of change of ECL in response to the concentration of immunoreactant. Applicants note that in this context, the term “rate” refers to the slope of a plot of ECL signal vs. concentration (e.g. see Figure 2 in Shibue et al.) and does not refer to the time dependence of a reaction. In fact, Shibue et al. fails to teach or suggest the measurement of the time course of a reaction or the measurement of ECL as a function of time. Accordingly, Shibue et al. does not anticipate the presently claimed subject matter.

14. Claims 37-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shibue et al.. (West abstract of EP500,305A2) taken in combination with the admitted prior art as set forth in the instant specification.

Applicants urge that Shibue et al., alone or in combination with the “Admitted Prior Art”, fails to teach or suggest the presently claimed invention. In order to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations [MPEP §2143].

Shibue et al. does not teach or suggest the presently claimed invention for the reasons set forth above. The teachings set forth in the "Admitted Prior Art" fail to compensate for the deficiencies of Shibue et al. More specifically, like Shibue et al., the Admitted Prior Art fails to teach or suggest the presently claimed method for determining the time course of reaction employing the measurement of emitted electrochemiluminescence.

15. *Claims 1-36 are allowed.*


Applicants would like to take this opportunity to thank the Examiner for indicating that claims 1-36 have been allowed.

In view of the amendments and remarks herein, the present application is believed to be in condition for allowance. Favorable reconsideration of the application is earnestly solicited. If further issues remain, the Examiner is respectfully requested to call the undersigned attorney.

Respectfully submitted,

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